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A cost-effectiveness analysis of modafinil therapy for psychostimulant dependence

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Abstract

Introduction and Aims. *To examine the cost-effectiveness of modafinil (200 mg daily) plus counselling compared with placebo for the treatment of psychostimulant dependence.* ***Design and Methods.*** *Cost and outcome data were collected alongside two randomised controlled trials of modafinil 200 mg daily over 10 weeks for methamphetamine (*n = 74*) and cocaine dependence (*n = 8*), respectively. Incremental cost-effectiveness ratios representing the additional costs to achieve a given outcome were calculated for both the change in the number of stimulant-free days and quality-adjusted life years 12 weeks post-treatment.* ***Results.*** *The incremental cost-effectiveness ratio indicated that it would cost an additional $AUD79 to achieve an extra stimulant-free day with modafinil compared with placebo. This result was not statistically significant, but appeared to be a robust estimate after sensitivity analysis. Counselling, whether received within program or from other services, improved the cost-effectiveness of modafinil relative to placebo.* ***Discussion and Conclusions.*** *Strategies to improve the uptake of counselling are recommended as cost-effective.* [Shearer J, Shanahan M, Darke S, Rodgers C, van Beek I, McKetin R, Mattick RP. A cost-effectiveness analysis of modafinil therapy for psychostimulant dependence. *Drug Alcohol Rev* 2010;29;235–242]

Key words: modafinil, psychostimulant treatment, methamphetamine dependence, cocaine dependence, cost-effectiveness.

Introduction

Psychostimulant dependence is a major public health problem in many parts of the world associated with a range of economic costs. There are no reliable estimates of the burden specifically attributable to psychostimulant use, although the cost of illness associated with illegal drug use is significant and growing in many parts of the world [1–4]. There are, however, several distinctive drivers of costs relevant to psychostimulant use. These include direct health-care costs, such as dental problems in methamphetamine users [5,6], cardiovascular disease [7,8], emergency room presentations often complicated by psychosis [9–11], poor mental and physical health (weight loss, sleep disturbance, depression), violence and blood borne viral risks [12,13]. Indirect costs encompass lost productivity because of psychostimulant mortality and morbidity, crime and incarceration. Psychosocial interventions have been the mainstay of treatment for psychostimulant problems. Approaches such as cognitive–behavioural therapy (CBT) and contingency management have demonstrated efficacy in reducing psychostimulant use in dependent users [14–17]. The effectiveness of psychosocial interventions is, however, limited by poor uptake and attrition rates [18]. There are currently no medications recognised as effective in reducing psychostimulant use in dependent patients [19].

A MEDLINE search identified only three published reports on the cost-effectiveness of treatment for cocaine dependence, and none in the area of methamphetamine dependence. The cost-effectiveness of providing housing and paid work skills training contingent

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on drug and alcohol abstinence was trialled in homeless cocaine users compared with day treatment plus unpaid vocational rehabilitation [20]. The program cost twice as much as treatment as usual; however, incremental costs per additional abstinent week were similar between the 6 and 12 month follow up at $US1019 and $US1007 (2000 costs). A cost-effectiveness analysis of two levels of prize-based contingency management estimated the additional cost to achieve an extra week of cocaine abstinence was $US75 (year unspecified) between standard treatment and the higher prize value condition [21]. A retrospective cost-effectiveness analysis of a trial of disulfiram 250 mg daily to treat cocaine use in methadone-maintained subjects estimated an incremental cost per additional day of cocaine abstinence of $US73 (1999 costs) [22].

Modafinil is a novel, non-amphetamine-type stimulant approved for the treatment of narcolepsy, shift workers syndrome and sleep apnoea-related fatigue. Modafinil appears to be well-tolerated, non-reinforcing and may have potential in the treatment of psychostimulant dependence [23–25]. Between July 2006 and September 2007 we conducted two concurrent randomised placebo-controlled trials of modafinil 200 mg daily in cocaine- and methamphetamine-dependent subjects at two sites in inner city Sydney, Australia. The results of the methamphetamine randomised controlled trial (RCT) have been reported elsewhere [26]. Here we examine the cost-effectiveness of modafinil in the treatment of psychostimulant dependence using prospective economic data collected alongside clinical data at one of the sites participating in the clinical trials.

Methods

Design, setting and subjects

This was a double-blind placebo-controlled study with 10 weeks of treatment and a 12 week follow up. Seventy-four methamphetamine-dependent and eight cocaine-dependent subjects were enrolled through a primary health-care centre that recruited and treated subjects participating in two concurrent RCTs of modafinil for methamphetamine dependence (modafinil $n = 34$, placebo = 40) and cocaine dependence (modafinil $n = 5$, placebo = 3), respectively.

Interventions and outcomes

Subjects were allocated to receive either 200 mg modafinil or placebo to be taken once daily before noon. Subjects were offered four sessions of a brief CBT intervention [27]. Data were collected at weekly medical reviews while subjects were in treatment and research interviews at baseline, at the end of the 10 week treatment period and 12 weeks after treatment. Primary outcomes were the change from baseline psychostimulant use measured by 28 day self-report based on prospective drug use diaries [28] and change from baseline in quality-adjusted life years (QALYs) measured by the EQ-5D [29]. The EQ-5D has been validated in chronic, heroin-dependent populations [30,31]. The outcomes were measured at 12 weeks post-treatment in order to capture relapse and other post-treatment effects.

Cost estimates

Cost data were collected on all health services used by all subjects over the 10 week treatment period. Time spent by personnel in direct clinical contact and non-face-to-face activities, such case conferencing and diagnostic tests, were recorded on forms placed in subjects' medical charts and pharmacy-dispensing records. Total time was recorded in minutes and valued using the relevant staff salaries with benefits. Overhead facilities costs were not collected as we were interested in marginal costs, and the small sample was unlikely to impact significantly on the overhead costs of the clinic. Data on other medications, both prescribed and over-the-counter, were also collected at the weekly medical reviews; however, this was unreliable because of high treatment dropout. Information on contact with other health professionals and diagnostic procedures was collected at research interviews. Missing data for other health service utilisation were imputed using average baseline values for each group [32]. Mean imputation is commonly used for health economic analysis as it overcomes problems of skewed data, caused by rare, but resource-intensive events, such as emergency department visits, which may be exaggerated by other forms of imputation. The perspective taken for this study was that of government, as care was provided in a public sector treatment centre. Prices were based on Australian government rebate schedules published by the Pharmaceutical Benefits Advisory Committee [33], the Pharmaceutical Benefits Scheme [34], the Medicare Benefits Schedule [35] and National Public Hospital Cost Weights [36]. The cost of modafinil was based on the price paid by the Australian Government under the Pharmaceutical Benefits Scheme for modafinil prescribed for narcolepsy. Costs were standardised into 2007 Australian dollars using the consumer price index [37].

Data analysis

Incremental cost-effectiveness ratios (ICERs) were calculated for two outcome measures (stimulant-free days, QALYs) at 12 weeks post-treatment. The ICER is defined as the between-group difference in average treatment costs divided by the between-group difference in average outcomes. Thus, the ICER reflects the additional expenditure required to gain an additional unit of outcome (stimulant-free days/QALYs) at a fixed time point (12 weeks post-treatment). Cost data are generally skewed, so bootstrapping methods were applied to the costs and effects for each treatment (from 1000 repeated samples) to produce 95% confidence intervals [38]. The resultant 1000 cost and effect pairs were plotted on the cost-effectiveness plane. When the distribution of the ICERs falls both in the negative and positive space a cost-effectiveness acceptability curve (CEAC) can assist with interpretation of the results. If the ICER falls below some given amount that decision-makers are willing to fund then the treatment should be implemented. The CEAC summarises the results as being cost-effective for all possible values [39–42]. The sensitivity of the findings was also examined by varying the underlying assumptions about costs and effect sizes under three scenarios (full overheads, methamphetamine users only and impact of counselling).

Results

Outcomes

The typical subject was male (61%), aged in the mid-thirties (mean age 35 years, range 20–53), relatively well-educated (63%) and half were employed. At baseline, subjects had used illicit psychostimulants on an average of 20 days in the past 28 days and had regularly used psychostimulant drugs for 7 years. There were no statistically significant between-group differences in demographics or drug use history at baseline. The mean change in stimulant use and QALY outcomes and 95% confidence intervals are summarised in Table 1. All outcome data were analysed on an intention to treat basis, with missing data imputed from baseline. The proportion of subjects lost to follow up at week 22 were similar between groups (modafinil 36%, placebo 42%, $P = 0.6$). There were no statistically significant between-group differences on either stimulant use ($U = 691$, $P = 0.15$) or QALYs ($U = 772$, $P = 0.5$). Mean QALYs were relatively high in both groups at baseline allowing little scope for detecting positive changes in quality of life. Baseline QALYs values for single-diagnosis psychostimulant users (0.94 ± 0.11) were significantly different from those of dual diagnosis opioid/psychostimulant users (0.72 ± 0.26) ($t = 4.72$, $P < 0.001$).

Resources

Subjects were scheduled to attend an initial medical assessment and 10 subsequent medical reviews involving doctors and nurses. In addition, four sessions were planned with drug and alcohol counsellors trained in the brief CBT intervention. Adherent subjects attended a hospital outpatient pharmacy to renew weekly prescriptions over the 10 week treatment period. Total health-care costs were calculated for each subject's documented treatment and other health-care resource use multiplied by prices and then summed (Table 2).

Direct treatment costs were significantly higher in the modafinil group (Table 2). The main cost difference was the additional cost of modafinil that averaged $AUD232 ± 137. There was, however, no significant difference in total costs after other heath-care costs were included. A higher proportion of hospital costs in the placebo group were attributed to 10% of the sample who were hospitalised for accidents ($n = 2$) or stimulant detoxification ($n = 2$).

Cost-effectiveness

Twenty-eight day stimulant use. The ICER, or the additional cost to achieve an additional stimulant-free day, was $AUD79. Confidence intervals were constructed around cost and outcome estimates from Tables 1 and 2 using bootstrapping. The incremental costs and incremental effects from the 1000 bootstrap re-sampled pairs were plotted on a cost-effectiveness plane (Figure 1). The CEAC (Figure 2) graphically represents the probability that modafinil was more cost-effective than placebo. When, as is the case here, both

Table 1. *28 day stimulant use and QALY change score by group at week 22*

Variable	Group	Mean[a]	95% CI[a]
Mean 28 day drug use change score	Modafinil ($n = 39$)	−6.92	−4.15, −9.80
	Placebo ($n = 43$)	−4.16	−1.39, −6.89
Mean QALY change score	Modafinil ($n = 39$)	+0.037	−0.040, +0.119
	Placebo ($n = 43$)	+0.043	−0.037, +0.126

[a] 95% CI estimated with bootstrap methods. CI, confidence interval; QALY, quality-adjusted life year.

Table 2. *Total cost for each group (10 week treatment), AUD2007*

		Modafinil (n = 39)	Placebo (n = 43)
Direct treatment costs			
Resource	Prices		
Medical Officer	$60.95 per hour	5 447	6 111
Nursing	$31.29 per hour	634	811
Counsellor	$32.27 per hour	626	496
Pharmacy	$36.22 per hour	1 259	1 607
Modafinil	$2.86 per 100 mg	9 049	0
Diagnostics	MBS rates	1 218	960
Total treatment costs		18 233	9 985
Mean direct treatment costs		467 (390, 549)[a]	232 (193, 273)[a]
Other health-care costs			
Resource	Prices		
Hospital service	PBAC rates	4 900	9 933
Medical service	MBS rates	2 833	3 229
Dental services	MBS rates	2 527	2 004
Psychosocial[b]	PBAC/MBS	4 977	2 851
Other services	MBS rates	536	1 381
Diagnostics	MBS rates	3 369	2 873
Total other health-care costs		19 142	22 271
Grand total		37 375	32 257
Mean total cost		960 (772, 1 242)[a]	742 (463, 1 203)[a]

[a] 95% confidence intervals estimated with bootstrap methods. [b] Includes psychiatrists modafinil $995 placebo $431. PBAC, pharmaceutical benefits advisory committee; MBS, medicare benefits schedule.

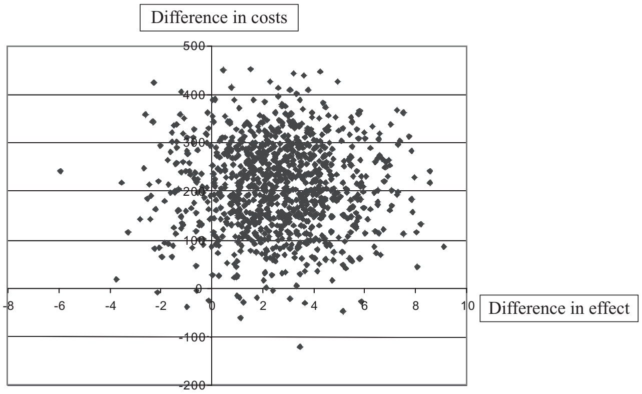

Figure 1. *Cost-effectiveness plane with 1000 bootstrapped incremental cost-effectiveness ratio re-samples of the difference in costs and 28 day drug use outcome pairs.*

costs and outcomes are greater in the modafinil intervention, the CEAC shows the probability that the decision to provide treatment at a given funding level is the correct decision, or in other words, the willingness to pay for each additional stimulant-free day. The CEAC provides more information about uncertainty than 95% confidence intervals in this case the curve shows a 70% interval exists between 15% and 85% defined as between $AUD35 and $AUD473 per stimulant-free day [42].

Quality-adjusted life years

Confidence intervals were constructed around cost and QALYs data from Tables 1 and 2 using bootstrapping. The incremental costs and incremental effects from the 1000 bootstrap re-sampled pairs are plotted on the cost-effectiveness plane in Figure 3. Here the sample sits around the central axis indicating no clear difference between modafinil and placebo in terms effectiveness.

Sensitivity analyses

Impact of overheads and training. As discussed in the methods, a full overhead costing approach was not undertaken. In order to test how this may have affected results, 28% was added to the direct treatment costs, and the ICER was recalculated (Table 3). The cost of a 1 day workshop to train counsellors in the brief CBT intervention was also incorporated in the analysis by dividing it by the number of counsellor minutes recorded. The addition of overheads and training costs made little difference to the between-group ICER estimates.

Single substance use diagnosis methamphetamine dependence. In the RCT, a post-hoc analysis of data limited to methamphetamine-dependent subjects with no other drug dependence (i.e. opioid patients were

Table 3. *ICER with and without facility overhead estimates*

Variation	Treatment	Variable	Mean (95% CI)[a]	ICER
Original ICER	Modafinil ($n = 39$)	Total costs ($AUD)	960 (772, 1242)	79
		Stimulant use change	−6.92 (−4.15, −9.80)	
	Placebo ($n = 43$)	Total costs ($AUD)	742 (463, 1203)	
		Stimulant use change	−4.16 (−1.39, −6.89)	
Additional 28% overheads and training costs apportioned	Modafinil ($n = 39$)	Total costs ($AUD)	1011 (830, 1294)	78
		Stimulant use change[b]	−6.92 (−4.15, −9.80)	
	Placebo ($n = 43$)	Total costs ($AUD)	797 (516, 1308)	
		Stimulant use change[b]	−4.16 (−1.39, −6.89)	

[a] 95% CI estimated with bootstrap methods. [b] Note effect size (stimulant use change) held constant. CI, confidence interval; ICER, incremental cost-effectiveness ratios.

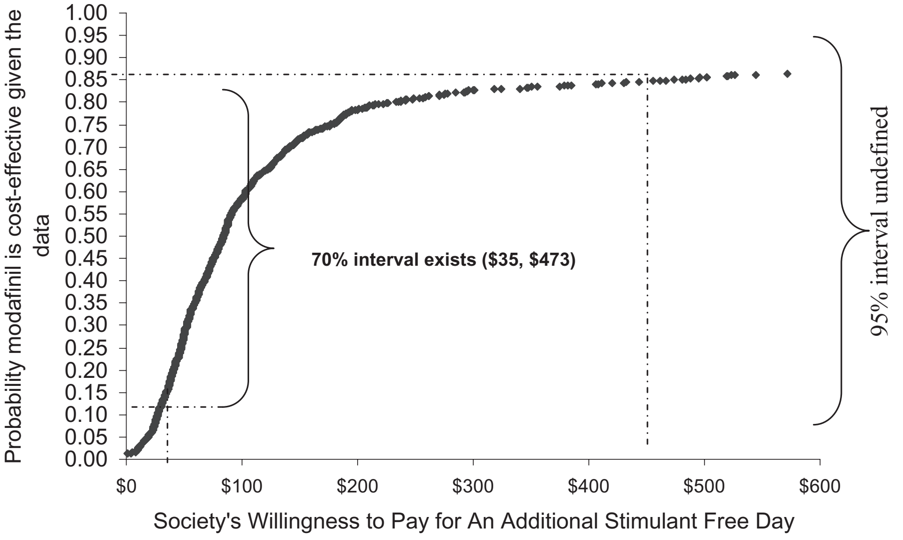

Figure 2. *Cost-effectiveness acceptability curve for modafinil versus placebo.*

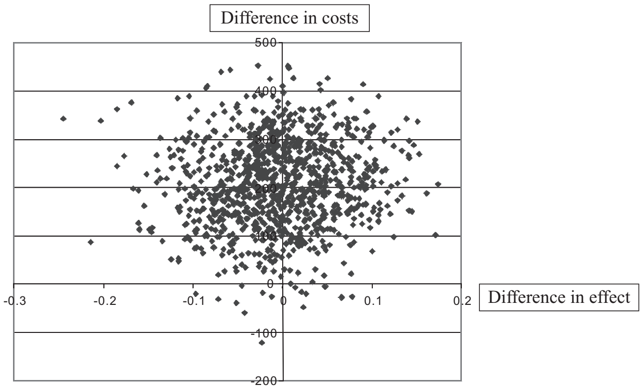

Figure 3. *Cost-effectiveness plane with 1000 bootstrapped incremental cost-effectiveness ratio re-samples of the difference in costs and quality-adjusted life year outcome pairs.*

excluded) found a statistically significant ($P < 0.05$) difference in 28 day stimulant use between modafinil and placebo at the end of treatment (week 10), but the difference was not significant at week 22 because of relapse. Accordingly, an ICER was calculated for single-diagnosis methamphetamine-dependent subjects, excluding eight cocaine-dependent subjects and four dual diagnosis opioid/methamphetamine-dependent subjects (Table 4). The ICER calculated for methamphetamine subjects of $AUD68 was marginally lower than the combined group ICER of $AUD79. A two-way sensitivity test was performed where additional overhead costs detailed in the first sensitivity analysis were applied to the single-diagnosis methamphetamine subsample. Again, this made little difference to the ICER calculation.

Impact of counselling. Modafinil plus counselling compared with placebo appeared to be more cost-effective

Table 4. *ICERs for single-diagnosis methamphetamine-dependent subjects*

Sample	Treatment	Variable	Mean (95% CI)[a]	ICER
Methamphetamine users	Modafinil (*n* = 33)	Total costs ($AUD)	963 (798, 1126)	68
		Stimulant use change	−6.85 (−2.85, −10.70)	
	Placebo (*n* = 37)	Total costs ($AUD)	750 (619, 894)	
		Stimulant use change	−3.73 (−0.89, −6.89)	
Methamphetamine users plus full overheads	Modafinil (*n* = 33)	Total costs ($AUD)	1015 (849, 1193)	69
		Stimulant use change[b]	−6.85 (−2.85, −10.70)	
	Placebo (*n* = 37)	Total costs ($AUD)	801 (676, 950)	
		Stimulant use change[b]	−3.73 (−0.89, −6.89)	

[a]95% CI estimated with bootstrap methods. [b]Note effect size (stimulant use change) held constant. CI, confidence interval; ICER, incremental cost-effectiveness ratios.

Table 5. *ICERs by group for those who received counselling and those who did not receive counselling*

Sample	Treatment	Variable	Mean (95% CI)[a]	ICER
Accessed counselling	Modafinil (*n* = 20)	Total costs ($AUD)	1087 (911, 1290)	64
		Stimulant use change	−9.35 (−5.95, −13.10)	
	Placebo (*n* = 23)	Total costs ($AUD)	886 (708, 1112)	
		Stimulant use change	−6.24 (−2.14, −10.55)	
Did not accessed counselling	Modafinil (*n* = 19)	Total costs ($AUD)	834 (720, 952)	98
		Stimulant use change	−4.34 (−0.63, −8.58)	
	Placebo (*n* = 20)	Total costs ($AUD)	590 (491, 685)	
		Stimulant use change	−1.86 (+1.47, −5.47)	
Accessed counselling plus full overheads	Modafinil (*n* = 20)	Total costs ($AUD)	1157 (969, 1360)	64
		Stimulant use change[b]	−9.35 (−5.95, −13.10)	
	Placebo (*n* = 23)	Total costs ($AUD)	958 (776, 1173)	
		Stimulant use change[b]	−6.24 (−2.14, −10.55)	

[a]95% CI estimated with bootstrap methods. [b]Note effect size (stimulant use change) held constant. CI, confidence interval; ICER, incremental cost-effectiveness ratios.

than modafinil without counselling compared with placebo (Table 5). Again, the addition of full overheads, including the counselling specific training costs, did not appreciably change the ICER estimate. Note that confidence intervals for all scenarios overlapped between groups for both costs and effects, indicating the need for more research data from larger sample sizes to confirm these findings.

Discussion

This cost-effectiveness analysis estimated that modafinil therapy for psychostimulant dependence had an incremental cost of $AUD79 for each additional stimulant-free day. From the perspective of economic decision making, there was a large degree of uncertainty around whether modafinil therapy would be cost-effective. More information is required from studies with larger sample sizes or meta-analysis to reduce the level of decision-making uncertainty. In any event, the question remains how much society is willing to pay for additional illicit stimulant-free days in this treatment population.

The study found no difference in the EQ-5D between modafinil and placebo, although it is doubtful whether the EQ-5D was sufficiently sensitive to detect changes in quality of life in this treatment population. The focus of the EQ-5D is on physical disability, and this did not appear to be a meaningful or sensitive measure in single-diagnosis psychostimulant users. The average QALY values at baseline were much higher than those reported in other drug treatment trials in alcohol [43] and heroin users [30] and may have been insensitive to subsequent changes in quality of life. Interestingly, EQ-5D scores were significantly lower among the dual dependence opioid/psychostimulant subgroup ($t = 4.72$, $P < 0.001$), which were closer to the scores reported in studies among heroin users. The significantly higher EQ-5D scores in subjects with dual opioid/psychostimulant dependence may be further evidence that physical impairment in psychostimulant users is often as a result of concurrent opioid use [44,45]. Future work in single-diagnosis psychostimulant users could usefully consider alternative quality-of-life measures with broader psychosocial components, such as the preference-weighted version of the SF-36, the SF-6D [46].

Sensitivity analysis found that the addition of any form of counselling to treatment generally achieved additional stimulant-free days at a low cost and could be recommended as a cost-effective strategy. The ICER for modafinil plus counselling was a third lower than for modafinil without counselling when both were compared with placebo, suggesting a positive pharmacotherapy/psychotherapy interaction effect that has also observed with bupropion and levodopa/cardidopa in cocaine dependence [47,48]. This finding gives further weight to the recommendation arising from the RCT to investigate methods to enhance the uptake of counselling. Otherwise, the sensitivity analysis found that the ICER estimates were robust with respect to variations in resource use and were modestly improved when the sample was limited to single-diagnosis methamphetamine-dependent subjects.

There are several limitations to the generalisability and validity of this cost-effectiveness analysis. RCTs are inherently unrealistic, and this is particularly true when it comes to the intensity of resources used. Given its low abuse liability and good safety profile, unsupervised modafinil therapy could be delivered in a primary practice model with only a fraction of the medical inputs documented in the present study. A treatment model similar to that for bupropion in smoking cessation could be feasible, consisting of an initial medical assessment and 2 week induction prescription with a follow-up medical consultation after 2 weeks and a prescription for the remaining 8 weeks [49].

The problems encountered in this cost-effectiveness analysis were not unexpected or unusual. As Briggs *et al.* [50] have pointed out, clinical trials are often designed to detect minimum clinically meaningful effect sizes, and therefore, values close to zero should not be unexpected. Small effect sizes are not insignificant, especially in areas, such as the pharmacological treatment of psychostimulant dependence, where no compounds to date have been definitively proven to be safe and effective in reducing psychostimulant use and associated problems.

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